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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/089,485 | 03/27/2002 | Ken-Ichi Hanada | 4239-62489 | 7424 |

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| EXAMINER | |
|---|---|
| CANELLA, KAREN A | |
| **ART UNIT** | **PAPER NUMBER** |
| 1643 | |

DATE MAILED: 04/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/089,485 | HANADA ET AL. | |
| | Examiner | Art Unit | |
| | Karen A. Canella | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☐ Claim(s) *1-3,5,7,8,14,25-28,31,37-39 and 42-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3,5,7,8,14,25-28,31,37-39 and 42-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *Jan 30, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claim 1, 5 and 48 gave been amended. Claims 49-51 have been added. Claims 1-3, 5, 7, 8, 14, 25-28, 31, 37-39, 42-51 are pending and under consideration.

Text of title 35, U.S. Code, not found in this action, can be found in a prior action.

The rejection of claims 1-3, 5, 7, 8, 14, 25, 26, 28, 31 and 42-48 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in light of applicants amendments.

The rejection of claims 1-3, 5, 7, 8, 14, 25-28, 31, 37-39, 42-48 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for the following reasons of record. Claims 49-51 are rejected for the same reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized by In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-3, 5, 7, 8, 14, 25-28, 31 and 42-48 are drawn to a method of treating a subject comprising administering an FGF-5 polypeptide to said subject. Claims 37-39 are drawn to a method of lysing a cell of a neoplasm in a subject comprising administering an FGF-5 polypeptide to said subject. The term FGF-5 polypeptide encompasses disclosed sequences of FGF-5 such as SEQ ID NO:6, 18 and 19, as well as variants of said sequences. Thus all claims require the treatment of a subject having a neoplasm expressing FGF-5, and a subset of claims requires treatment by variants of FGF-5 which are speculated upon by the specification, but not disclosed (pages 32-38). The specification teaches that an isolated T-cell clone 2 was isolated from a regressing metastatic lesion from a renal cell carcinoma (page 23, lines 18-23). The specification teaches that said clone 2 recognized an antigen shared between renal cell carcinomas, and that this recognition was restricted to HLA-A3+ (page 24, lines 7-25). The specification also teaches that the Clone 2 CTL response was directed to a non-mutated epitope within the FGF-5 (page 26, lines 7-13). The specification does not provide objective evidence that a Clone 2 CTL response can be generated in vivo which would actively lyse FGF-5 expressing tumor cells in vivo.

The art teaches that administration of a tumor associated peptide can generate a quantifiable CTL in the peripheral blood of cancer patients, such a CTL response is not associated with clinical evidence of tumor regression (Lee et al, Journal of Immunology, 1999, Vol. 163, pp. 6292-6300). Further, Ohlen et al (Journal of Immunology, 2001, Vol.166, pp. 2863-2870) teach that T-cells recognizing normal proteins expressed in tumors can be isolated in vitro, but that the existence of said T-cells does not preclude in vivo anergy induction and deletion (page 2863, second column, lines 1-6 of the last paragraph). Antoinia et al (International Immunology, 1995, Vol. 7, pp. 715-725) teach that T-cells which are impaired in the ability to proliferate in response to antigen and unable to reject tumors in vivo were fully functional as CTL lymphocytes in vivo (page 724, first column, first full paragraph). These references serve to demonstrate that the lysis or "recognition" of target cells expressing a FGF-5 antigen in vitro does not constitute evidence that said T-lymphocytes would be effective at lysing tumor cells in vivo.

The prior art teaches that tumor cells are phenotypically less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen

processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower immune response, failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the tumor due to the stromal barrier (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4). The specification has provided evidence that a T-cell clone is able to recognize tumor cells expressing an epitope of the claimed tumor rejection antigen precursors in vitro. Paul teaches that lymphocytes from tumor bearing patients have frequently been found to be cytotoxic to their own tumor cells in vitro, but that this effect was blocked by the addition of sera from said patients. Paul teaches that the constituent of the sera which caused the blocking of the cytotoxicity was unknown, but that antibodies, antibody-antigen complexes and shed antigen have all been implicated in the blocking phenomenon (Paul page 1167, second paragraph under the heading "Immunological Enhancement and Blocking Factors"). Paul also notes that in some cases, immune response to a tumor antigen may sometimes stimulate the growth of the tumor cells directly (last line under the heading "Immunological Enhancement and Blocking Factors", page 1167). With respect to the blocking factor found in serum, Apostolopoulos et al (Nature Medicine, 1998, vol. 4, pp. 315-320) teach that endogenous antibodies present at the time of administration of a tumor peptide re-routes the immune response from a cellular response to a humoral response. In pre-clinical experiments with mice, MUC1 peptides targeted to the mannose receptor produce high levels of CTL and a low level of antibodies. However, in human clinical trials a low level of CTL and a high level of humoral response was observed (Apostolopoulos, page 315, first column, bridging paragraph). Apostolopoulos et al teach that the presence of endogenous antibodies which bind to the MUC1 peptide was responsible for this re-routing of the immune response from cellular to humoral due to the Fc portion of the antibody (page 319, first column, lines 7-10). Apostolopoulos et al teach that mice are devoid of these antibodies (page 315, second column, lines 9-13) and are thus able to effectively mount a cellular immune response against the target antigen. Apostolopoulos et al teach that these findings have implication for other immunotherapy approaches (page 318, lines 4-8, under the heading "Discussion". In support of these conclusions Jager et al (PNAS, 2000, Vol. 97, pp. 12198-

12203) teach that patients who do not have antibodies to the cancer testis antigen, NY-ESO-1, were able to generate a specific T-cell response to NY-ESO after intradermal administration, whereas patients having antibodies prior to treatment which reacted with said antigen already had T-cells which reacted with target cells expressing said antigen in vitro, and said positive patients did not develop significant CTL in response to the administered NY-ESO antigen. These references serve to demonstrate that the induction of a anti-tumor CTL response after the administration of a tumor peptide is unpredictable.

Paul (ibid) states that deficient antigen presentation is a mechanism by which tumor cells escape immune detection. This is corroborated by the observations set forth in the abstracts of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993, Vol. 7, pp. 99-105 and the abstract of Algarra et al, International Journal of Clinical and Laboratory Research, 1997, Vol. 27, pp. 95-102) which all teach that primary tumors in situ are often heterogeneous with respect to MHC presentation. The effect of the claimed vaccine upon such a heterogeneous tumor has not been demonstrated by the specification. More currently, Bodey et al (Anticancer Research, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teaches that the failure of methods of treating cancer comprising the administration of tumor antigens is due to the failure of cancer vaccines to eliminate the most dangerous cells within a tumor which are so de-differentiated that they no longer express cancer cell specific molecules.

Further, the instant claims encompass methods reliant upon fragments and variants of FGF-5. The specification teaches that SEQ ID NO:6 is a target of the Clone 2 CTL which recognizes SEQ ID NO:6 in the context of HLA-A3+. The specification does not provide objective evidence that a fragment of FGF-5 is the target for any other CTL which recognizes FGF-5 in the context of a non-HLA-A3+ context. The art teaches that MHA/peptide binding predictions are not sufficient for identifying CD8 T cell epitopes (Pelte et al, Journal of Immunology, 2004, Vol. 172, pp. 6783-6789). There is no nexus between the recognition of FGF-5 in the context of HLA-A3+ and the recognition of FGF-5 in the context of non-HLA-A3+, thus one cannot reliably construe that FGF-5 on the surface of a tumor cell would be a target for a non-HLA-A3+ restricted T-cell. The specification does not teach how to make variants of FGF-5 that would function in a method of treating a subject, thus one of skill in the

art would be subject to yet another degree of undue experimentation in order to practice the broadly claimed invention.

Due to the unreliability of the art as discussed above, the lack of a working example which demonstrates the successful treatment of a subject with an FGF-5 expressing tumor, and the breath of the claims as including variants and numerous fragments of FGF-5, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the claimed invention.

Applicant argues that a clinical trail with human patients having FGF-5 positive renal cell carcinomas is currently ongoing. Applicant states that the results of the clinical trail are not yet available due to the fact that survival time for these patients is measured in months to years. Applicant maintained that the administration of the HLA-A3+ or HLA-A2+ epitope peptide sequences does stimulate an immune response in said patients. This has been considered but not found persuasive. It is noted that the claims are drawn to a method of treating a subject by stimulating a CTL response. thus it would be necessary to evoke a clinically objective response which is directed to overall survival time or disease free survival time or other parameter which could benefit a patients having a neoplasm expressing FGF-5. A declaration including actual evidence of objective clinical response in patients having RCC after administration of DEQ ID NO:6, 19 or 18, as indicated in new claims 49-51. Further, the claims are draw to any neoplasm expressing FGF-5, rather than only renal cell carcinoma, and there is no guarantee that FGF-5 expression in the context of HLA would be present to the same extent on other neoplasms beyond that of renal cell carcinoma because, as stated above (Paul, and the abstract of Semino et al and abstract of Algarra et al), cancer cells are known to downregulate the expression of MHC antigens in order to escape immune detection. Further, the claims encompass FGF-5 variant peptide sequences.

The M.P.E.P.(2164.03) teaches that

*in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving*

*unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.*

Because of the unpredictability of the art of treating cancer by immunotherapy as set forth in the rejection above and in the previous Office action, support in a Declaration under CFR 1.131 for distinct FGF-5 peptides as evoking a therapeutically effective response in renal carcinoma patients will not provide a nexus for enabling the full scope of the claims including variant FGF-5 peptides and treatment of other types of FGF-5 expressing neoplasms.

All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicants amendments.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
4/14/2006

KAREN A. CANELLA PH.D
PRIMARY EXAMINER